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Standardization of the Body Surface Area (BSA) Formula to Calculate the Dose of Anticancer Agents in Japan

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Background: The importance of deciding the appropriate dose of anticancer agents cannot be overemphasized. Body surface area (BSA) has been used to calculate the dose in anticancer therapy since the 1950s. Japanese oncologists, often use their own Japanese BSA formula instead of western BSA formulae. However, it is not widely known that some discrepancies exist between the BSA products of the Japanese and western styles. On the other hand, recently dose-calculations according to BSA were criticized from the standpoint of pharmacokinetics (PK). Lately, we have had many opportunities for international collaborations, which make it necessary to review these BSA formulae, and the BSA-based dosing method. A unified BSA formula in cancer therapy is needed in Japan.

Methods: We searched and compiled frequently used BSA formulae across the world using the MEDLINE search, oncology text, a web search on cancer clinical trial groups, and personally communicated with medical oncologists from western countries. Using these formulae, we calculated BSA for a typical Japanese individual, and compared their products. We calculated BSA using these formulae for individuals of widely varying physique, from 140 to 185 cm in height, and from 30 to 96 kg in weight, and estimated the amount of discrepancies among them.

Results: Among the various BSA formulae used in western countries, the DuBois formula is the standard. In Japan, the Fujimoto formula has been used frequently. The Fujimoto formula was based on a study of 201 Japanese subjects in 1949. For the average Japanese individual, the BSA calculated using the Fujimoto formula was about 3% lower than that which was calculated by western formulae. The BSA calculated for all heights and body weights using the Fujimoto formula, ranged between 0.7 and 4.8% less than those calculated by using the DuBois formula. The other western formulae showed larger discrepancies than the Fujimoto and DuBois formulae.

Conclusion: BSA-based dosing has failed to standardize the variation in PK for most anticancer agents, and individual dosing techniques are currently being investigated. However, until their clinical utilities are confirmed, it is necessary to depend on the BSA-based calculation for determining the dose of most anticancer agents. The DuBois formula, which is the western standard formula, is validated to a greater extent and its accuracy has been confirmed more than others, including the Fujimoto formula. We recommend the use of the DuBois formula instead of the Fujimoto formula in cancer chemotherapy and propose the standardization of this formula in Japan.

Key words: body surface area – dose – calculation – pharmacokinetics – anticancer agents

INTRODUCTION

It is very important to determine the appropriate dose of anticancer agents. Individuals have varying abilities to metabolize and eliminate drugs, and therefore the same dose of anticancer agents will have different pharmacokinetics (PK) and pharmacodynamics (PD). In addition, there is a presumed narrow therapeutic index for most anticancer agents. Reducing the dose of these agents not only reduces toxicity but also the effects on the tumor. This has been shown in breast cancer (1,2), testicular cancer (3), lymphoma (4), and other cancers. It is necessary to balance the ability of the normal tissue to withstand insult and the intrinsic sensitivity of the tumor. Selecting doses of anticancer agents to treat cancer patients can be a challenging decision for medical oncologists.

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Table 1. Search results on the BSA formulae

Author	Year of publication	No. of Patients	Formula
DuBois and DuBois (7)	1916	9	$BSA = 0.007184 \times H^{0.725} \times W^{0.425}$
Boyd	1935	411	$BSA = 0.017827 \times H^{0.5} \times W^{0.4838}$
Gehan and George (9)	1970	401	$BSA = 0.0235 \times H^{0.42246} \times W^{0.51456}$
Haycock et al. (10)	1978	81	$BSA = 0.02465 \times H^{0.39646} \times W^{0.5378}$
Mosteller (11)	1987	*	$BSA = \sqrt{H} \times W/3600$
Takahira (5)	1925	Unknown	$BSA = 0.007241 \times H^{0.725} \times W^{0.425}$
Fujimoto (5)	1968	201	$BSA = 0.008883 \times H^{0.663} \times W^{0.444}$

*Conducted by modifying the Gehan and George formula.

In cancer chemotherapy, the doses of chemotherapeutic agents are generally calculated using the body surface area (BSA). Various studies have estimated BSA, and currently several BSA formulae are being used across the world. In Japan, the Fujimoto BSA formula (5), is often used to calculate the dose of anticancer agents in practice or in clinical trials. The Fujimoto formula was first reported approximately forty years ago, and has been subject to the criticism that it may not be suitable for modern Japanese people. Recently, we have had several opportunities for international collaborations and thus we need to standardize the BSA formula. Therefore, we reviewed the BSA formulae and BSA-based anticancer agent dosing, and examined the validity of the Japanese BSA formula.

METHODS

We searched and compiled the frequently used BSA formulae across the world using the MEDLINE search, oncology text, a web search on cancer clinical trial groups, and personally communicated with medical oncologists from western countries. Using these formulae we calculated BSA for a typical Japanese individual, and compared their products. We performed calculations using these formulae for individuals of widely varying physique ranging from 140 to 185 cm in height, and from 30 to 96 kg in weight, and estimated the amount of discrepancies among them.

RESULTS

There were two method groups calculating BSA. The first group utilized both body height and weight. These had the same functional form, that is, $BSA = a0 \times H^{a1} \times W^{a2}$, with different coefficient values. The BSA calculations of the second group did not utilize the preceding formula, and chiefly utilized only body weight. The latter formulae have not been utilized in calculating the dose of anticancer agents because of their inaccuracy (6). Our search results showed seven representative BSA formulae of the former type (Table 1). Among them, the DuBois and DuBois (7), Boyd (8), Gehan and George (GG) (9), Haycock, Schwarta and Wistosky (10) and Mosteller (11) formulae were from western countries, while the Takahira and Fujimoto formulae (5) were from Japan. Among the clinical trial groups, for example, the Southwest Oncology Group (SWOG), described in its policy that the BSA can be determined from weight and height using a nomogram found in standard references (12). The DuBois formula has been used as the standard formula in western countries (13). The Cancer Therapy Evaluation Program (CTEP) in the United States of America has decided not to recommend any particular formula to be used for BSA-based dose calculation in NCI-sponsored treatment trials (12). The Gynecology Oncology Group's (GOG) statistical and data center has adopted western formulae such as the DuBois, Mosteller, Gehan, and Haycock formulae (14), whereas the Japan Clinical Oncology Group (JCOG) has adopted the Japanese Fujimoto formula (15).

For example, in the case of a patient whose height was 170 cm and body mass index was 22 kg/m^2, the BSA calculations using the western formulae and the Takahira formula resulted in similar products, that is, ranging between 1.73–1.75 m^2 (the DuBois formula was at 1.74 m^2). However, for the same example, the BSA calculated using the Fujimoto formula was 1.69 m^2, which was about 3% lower than the others.

Figure 1 graphically displays the discrepancies between the respective formulae and the Fujimoto formula, which is frequently utilized in Japan. Compared to the Fujimoto formula, the Boyd, GG, Haycock and Mosteller formulae have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. Among these examples, the maximal overestimation was 0.2 m^2 by the GG formula and the maximal underestimation was 0.096 m^2 by the Haycock formula. The discrepancies between the DuBois and Fujimoto formulae ranged between 0.013 m^2 (0.9%) in the shortest and most obese patient (140 cm, 96 kg) and 0.061 m^2 (4.7%) in the tallest and thinnest patient (185 cm, 30 kg). This discrepancy between the DuBois and Fujimoto formulae was smaller than the discrepancies between other western formulae and the Fujimoto formula.

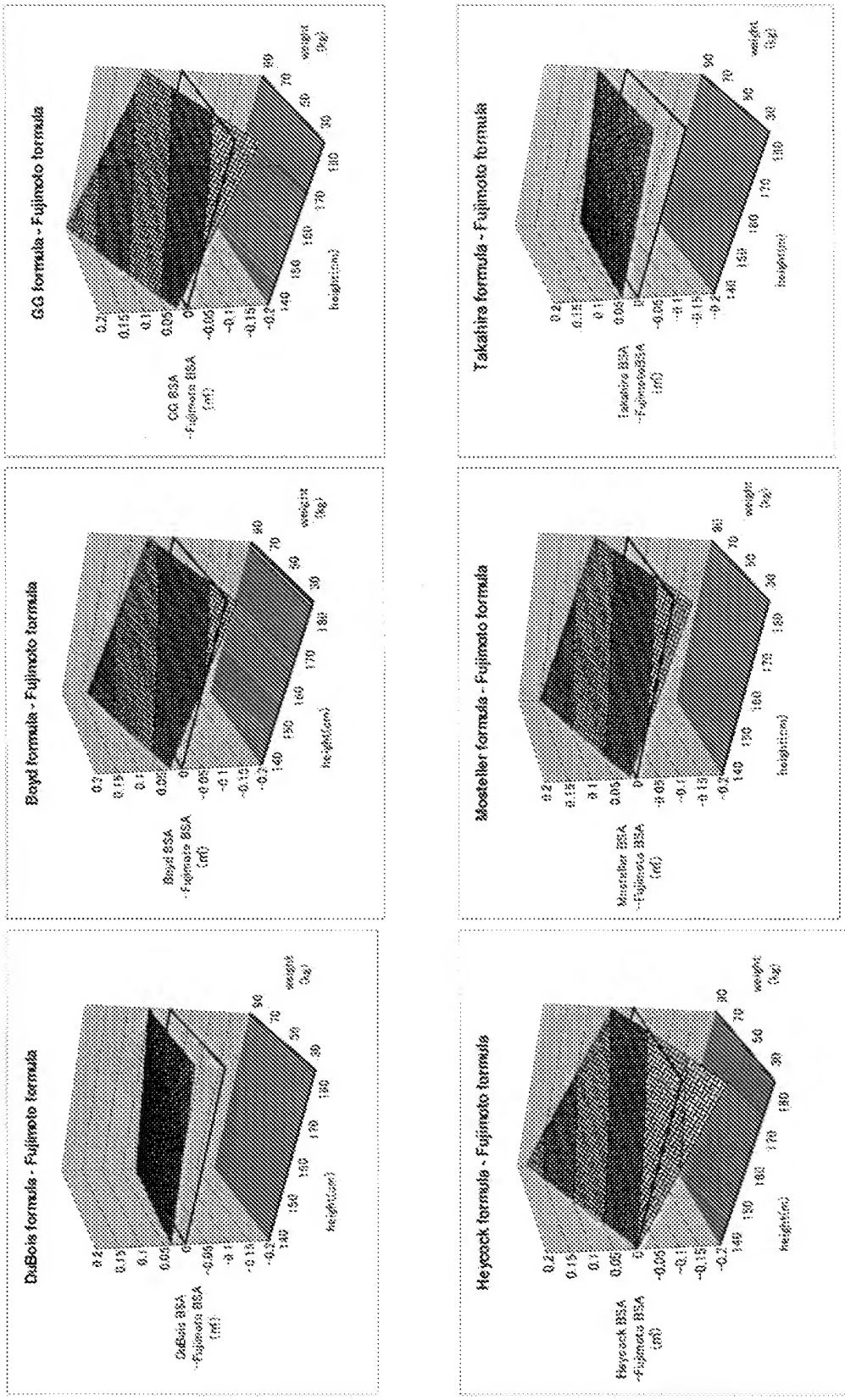

Figure 1. The discrepancies among respective formulae and the Fujimoto formula. The Boyd, GG, Heycock and Mosteller formulae tend to overestimate the BSA of short and obese patients and to underestimate the BSA of tall and thin patients compared to the Fujimoto formula. The discrepancies between the DuBois and Fujimoto formulae range between 0.013 m^2 (0.9%) in the shortest and most obese patient (140 cm, 96 kg) and 0.61 m^2 (4.7%) in the tallest and thinnest patient (185 cm, 30 kg). These discrepancies are smaller than the discrepancies among the other western formulae and the Fujimoto formula.

DISCUSSION

In 1916, DuBois and DuBois reported the BSA formula with direct measurements of nine subjects including a 36-year-old cretin, with an underdeveloped physique, a 12-year-old boy, a tall, thin adult male, and a short, obese adult female (7). In 1935, Boyd reported a formula as a result of investigating 411 subjects (8). In 1970, Gehan and George reported another formula based on the study of 401 subjects (9), and in 1978, Haycock, Schwarta and Wistosky reported another formula based on the measurements of 81 Caucasian, African American and Hispanic subjects (10). In 1984, Martin et al. determined the BSA from 20 aged cadaver subjects by planimetry on paper tracings of dissected skin and compared the measured surface area with the BSA predicted by the DuBois formula. They concluded that the predicted BSA did not differ significantly from the measured surface area and recommended continued use of the DuBois formula (16). In 1987, Mosteller modified the GG formula and simplified it to enable calculation using a pocket calculator (11). This formula has become popular because it is easy to use. In 1992, Wang et al. attempted to determine the accuracy of the BSA formulae proposed in these studies and examined their applicability to patient populations such as neonates and parturients (6). They directly measured the surface area with 60 pregnant women (34 to 40 week gestation) and 148 neonates. Regardless of these highly varying statures, the DuBois formula and other western formulae adequately predicted the measured surface area and they finally recommended the DuBois formula as a standard formula. However, their study did not include the Japanese formulae described below.

In Japan, Takahira et al. (in Fujimoto et al., Ref. 5) considered the DuBois formula inappropriate for Japanese individuals and constructed a new formula based on predetermined conditions, in 1925. In 1968, Fujimoto et al. (5) reported their formula with the direct measurement of 201 subjects, dividing them into three major age groups, namely, infants, children and adults. The Fujimoto formula for adults is one of the most commonly used formulae to calculate the dose of anticancer agents in Japan.

For a typical case where the height was 170 cm and the body mass index was 22 kg/m^2, the five western formulae and the Takahira formula calculations resulted in similar BSA products. However, compared with the other formulae, only the Fujimoto formula underestimated BSA by about 3%. Therefore, it was suggested that the anticancer agents might be underdosed in Japanese patients when using the Fujimoto formula.

BSA was calculated for individuals of widely varying physique from 140 to 185 cm in height, and from 30 to 96 kg in weight. The amount of discrepancies among these formulae was estimated. Since Japanese oncologists frequently use the Fujimoto formula, we evaluated the discrepancies between the Fujimoto formula and the six other formulae. Compared to the Fujimoto formula, the Boyd, GG, Haycock and Mosteller formulae have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. The discrepancy between the Fujimoto and DuBois formulae was relatively smaller than the discrepancies between the Fujimoto formula and other western formulae.

At present, dose calculations of most anticancer agents are made using BSA. BSA-based cancer chemotherapy began about a half century ago. In 1958, Pinkel (17,18) examined previous studies and determined the conventional pediatric and adult doses for five cytotoxic agents (Mercaptopurine, Methotrexate, Mechlorethamine, Triethylenethiophosphomide, and Actinomycin). For the same drugs, the appropriate therapeutic dose, for experimental animals was also determined from literature. These doses, per unit BSA, were calculated using a representative BSA, estimated using the DuBois formula for humans (7), and for the Meeh's formula for animals (5), which were then compared. It was found that similar values for the doses per unit surface area were obtained for each agent. Then, the use of BSA was recommended for performing dose calculations in chemotherapy. Since the publication of this report, the use of BSA for dose calculations of cytotoxic chemotherapy has become a standard practice.

However, this BSA-based dose calculation was recently criticized (19–22) because it failed to standardize the interpatient variation in PK. PK was analyzed in etoposide (23), calboplatin (24), epirubicin (25), paclitaxel (20), cisplatin (26), CMF (cyclophosmamide, methoterexate, and 5-fluorouracil) (27) and the other anticancer agents or combinations thereof and showed significant interpatient variability regardless of BSA-based dose calculations. With regards to cisplatin, Felix reported a mean plasma clearance of unbounded cisplatin with an interpatient variability of 25.6% (in Moore et al., Ref. 26) and showed that BSA-based dosing did not decrease the variability of unbounded cisplatin clearance. However, Bruno et al. (in Calvert et al., Ref. 28) showed that the variation of docetaxel clearance correlated with BSA. On the whole, most investigators reported that BSA did not correlate with the PK of most anticancer agents.

Besides the BSA-based calculations, several other individual dosing techniques have also been investigated. Calvert et al. (28) showed that the glomerular filtration rate (GFR) alone can predict area under the curve (AUC) for calboplatin, independent of BSA. The dose-calculation formula using patients' GFR was devised to predict AUC for calboplatin. Yamamoto et al. (29) reported that docetaxel clearance did not correlate to BSA and showed that it could be predicted by measuring 6-β-hydroxycortisol after cortisol administration. The possibility of a decrease in the variability of PK and PD by individual dosing of docetaxel is currently being investigated in a prospective trial. However, the complexity of metabolism and elimination of most other cytotoxic drugs makes the deviation of simple formulae difficult, and definitive evidence is awaited.

Therapeutic drug monitoring (TDM) and pharmacological adaptive control has been investigated for some anticancer agents. Methotrexate was one such example. Evans et al. (30) showed, in a prospective trial, that adjusting the dose of methotrexate with TDM to account for the patient's ability to clear

the drug could decrease the variability of PK and moreover, it could improve continuous complete remission in children with B-lineage acute lymphoblastic leukemia. However, TDM can be utilized in the second or later course of chemotherapy because the PK data of the previous course is necessary. Therefore, this technique cannot be used to determine the initial dose, unless a test dose is administered. Further, the introduction of TDM into clinical practice would be difficult because of its cost and inconvenience. Until these problems are overcome or individual dosing techniques are developed, we have to depend on the BSA-based dose calculations for most anticancer agents.

To summarize, the Fujimoto formula is frequently used in Japan. Though this formula was proposed over forty years ago, with the study of 206 Japanese patients, no recent studies have supported the validity of this formula, especially with regard to the modern Japanese physique which has become similar to that of people in western countries. The Takahira formula is not popular and has not been validated. As mentioned above, the results of the Boyd, GG and Haycock formulae showed larger discrepancies as compared with the Fujimoto and DuBois formulae. The DuBois formula has been a standard formula in western countries. Several studies have validated the accuracy of this formula (6,16,19). There was a relatively small discrepancy between the Fujimoto and DuBois formulae. However, the possibility of anticancer agents being underdosed is higher in the Fujimoto formula compared to the DuBois formula. In this age of international collaboration there is a need for a universal cancer treatment. It is therefore necessary to standardize the BSA formula to avoid the complexity of using multiple formulae. We recommend the DuBois formula as the standard BSA formula to calculate the dose of anticancer agents in Japan.

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